REMARKS

Claims 1-4 currently appear in this application. The Office Action of October 20, 2004, has been carefully studied. These claims define novel and unobvious subject matter under Sections 102 and 103 of 35 U.S.C., and therefore should be allowed. Applicants respectfully request favorable reconsideration, entry of the present amendment, and formal allowance of the claims.

Information Disclosure Statement

In accordance with the Examiner's requested, submitted herewith are copies of references AD, AH, AK, AM and AO.

Rejection under 35 U.S.C. 112

Claim 1 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The Examiner alleges that the claim contains new subject matter.

This rejection is respectfully traversed. Support for "under physiologic ionic conditions..." can be found in the specification as filed at page 9, lines 3-8; at page 21, lines 9-14, and ion Figure 6.

Claim 2 is rejected under 35 U.S.C. 112, first paragraph, because the Examiner states that the specification

does not provide enablement for inhibiting any and all metastases and any and all tumor growth.

This rejection is respectfully traversed. Claim 2 has now been amended to recite that the fragment inhibits **lung** tumor growth.

Claims 1-4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite. Claim 1 is said to be indefinite in the recitation "preparing Lys-plasminogen from human plasminogen either by adding plasminogen to a solution..."

This rejection is respectfully traversed. Claim 1 has been amended to recite adding **plasmin** to a solution of...

Art Rejections

Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Reich et al., U.S. Patent No. 5,288,489.

This rejection is respectfully traversed. The herein claimed Lys-Lys binding site I is well distinguished from the product disclosed in Reich et al.

The Lys-Lys binding site I claimed herein, has the activity to inhibit lung tumor metastasis and lung tumor growth it has substantially no activity to inhibit growth of endothelial cells of blood vessels. This Lys-Lys binding site I has not glycosylation, involves a special high-order structure, and binds intensely to heparin. None of these features has been disclosed or suggested by Reich et al.

These three features are closely related to each other. That is, the biological activity of the claimed fragment is based on its special high-order structure that may be established without glycosylation. Moreover, a special high-order structure is associated with an ability of the fragment to bind intensely to heparin.

The process for preparing the plasminogen fragment of the present invention comprises, as claimed in claim 1 and concisely listed therein, the following steps:

a. preparing Lys-plasminogen from human plasminogen either through the action of plasmin or autolysis;

b. treating the obtained Lys-plasminogen with elastase to produce fractions of fragments comprising Kringle 1 to Kringle 3; and

c. identifying the fragment which binds to heparin.

As originally filed, the process of the present invention is described in the paragraphs bridging pages 5 and 6 and of pages 12 and 13 of the specification as filed:

1. Plasminogen is treated with plasmin, etc. to produce Lys-plasminogen;

2. a solution containing Lys-plasminogen is treated with elastase to give **fractions of**

fragments comprising Kringle 1 to Kringle 3; and

3. **among the fractions obtained, a fraction having a strong heparin binding activity is selected to give a desired plasminogen fragment having the ability to inhibit tumor metastasis and growth**.

Treatment of Lys-plasminogen with elastase in step (b) provides a number of **different** fragments, although they all comprise Kringle 1 to Kringle 3. Indeed, when a solution obtained after treating Lys-plasminogen with elastase was subjected to heparin affinity chromatography, three distinct fractions were observed, *i.e.*, (i) fractions with **no** heparin binding activity; (ii) fractions with a **moderate** heparin binding activity; and (iii) fractions with a **high** heparin binding activity, corresponding to peaks A, B and C in Figure 3, respectively. This is also described in Example 5, particularly at page 20 of the specification as filed. The three classes of fractions obtained are distinct from each other in their capacity to bind heparin, although all fractions from the three classes commonly comprising Kringle 1 to Kringle 3 (namely, structurally similar although distinct in the presence or absence of glycosylation, and hence in molecular weight). Among the fractions obtained, the

fractions with a **high** heparin binding activity (no glycosylation, lowest molecular weight), *i.e.*, peak C in Figure 3, is selected as a desired plasminogen fragment having the ability to inhibit tumor metastasis and growth. As demonstrated in Declaration I previously submitted, **the fractions with low or no heparin binding activity [hence with no glycosylation, lower molecular weight], though these fractions were included in the solution obtained after treatment of Lys-plasminogen with elastase, failed to exhibit any activity in inhibiting tumor metastasis and growth, *i.e.*, no desired activity.**

Reich et al. disclose a Lys-Lys binding site I consisting of Kringle 1 to Kringle 3 which is derived from Glu-plasminogen by limited proteolysis, catalyzed by plasmin, whereby a peptide fragment is cleaved from the amino terminal domain. However, it should be noted that **the process disclosed in Reich et al. is the same as the herein claimed process up to step (b), *i.e.*,** treatment of Lys-plasminogen with elastase. However, Reich et al. **are silent with respect to step (c), *i.e.*,** selecting or screening for the desired fraction with a high heparin binding activity, which step, however, in the present invention, is the most important. Moreover, it appears that Reich et al. do **not** appreciate that proteolysis of Lys-plasminogen with elastase provides number

of different fractions of fragments, such as the fractions (i) to (iii) mentioned above with no, moderate, or high heparin binding activity, respectively. Reich et al. erroneously consider that the proteolysis produces a **single** molecular species as the claimed Lys-Lys binding site I consisting of Kringle 1 to Kringle 3. In conclusion, it is clear that the product obtained by Reich et al. would never inhibit lung tumor metastasis and lung tumor growth, nor inherently have the molecular weight claimed herein, lack of glycosylation, or heparin binding activity.

In view of the above, it is respectfully submitted that the claims are now in condition for allowance, and favorable action thereon is earnestly solicited.

Respectfully submitted,

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